# The Impact of Insulin Degludec on Glucocorticoid-Induced Hyperglycemia in Patients with Diabetes and COVID-19 Infection

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## Abstract

**Objective:** The objective was to assess the effectiveness and safety of insulin degludec (IDeg) on glycemic control in people with diabetes (PWD) hospitalized for moderate-to-severe coronavirus disease 2019 (COVID-19). **Design:** This study is a retrospective cohort study. **Setting and Participants:** Data were retrieved from medical records of PWD hospitalized for moderate-to-severe COVID-19. All patients who had steroid-induced hyperglycemia (SIH) were initiated with basal-bolus regimen with IDeg and human actaprid (HA) as part of their standard of care during admission. Data records at admission and discharge were retrieved and analyzed for hyperglycemia, insulin status, hypoglycemia, and other adverse events. The sigma plot version 15.0 was used to perform the statistical analysis and a *P* value (<0.05) was considered statistically significant. **Results:** The study retrieved data from medical records of 48 PWD hospitalized for moderate-to-severe COVID-19 and SIH for an average of 6.8 ± 2.5 days. There was a statistically significant decrease in average fasting plasma glucose from baseline (231.2 ± 91.1 mg/dL) to day 7/discharge (150.7 ± 32.1 mg/dL) ($P < 0.05$). The postprandial glucose showed a nonsignificant decrease; corresponding values were 295.0 ± 118.4 and 223.7 ± 65.4 mg/dL, respectively. The average IDeg dose increased significantly from baseline to day 7/discharge (15.6 ± 5.0 and 20.1 ± 6.5 units, respectively; $P < 0.05$). There was nonsignificant increase in average HA dose from 53.1 ± 16.7 IU on day 1 to 59.8 ± 16.6 IU on discharge day. No adverse events were reported in the medical records during hospitalization. **Conclusion:** IDeg is an effective and safe insulin for managing hyperglycemia in PWD who developed SIH during hospitalization for moderate-to-severe COVID-19.

**Keywords:** Basal insulin analogues, COVID-19, glucocorticoids, insulin degludec, SARS-CoV-2, steroid-induced hyperglycemia

## Introduction

The coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease 2019 [COVID-19] pandemic), caused severe acute respiratory illness, and it had an aggressive course in India due to high prevalence of diabetes.[1-3] One of the recognized major risk factors for increased morbidity and mortality during COVID-19 infection is poor glycemic control.[2,4-6] This is a major concern in India as a study reported slightly more than two-thirds of Indians with diabetes (76.6%) had poor glycemic control.[7]

Glucocorticoids are one of the recommended standard of care (SOC) in patients with moderate-to-severe COVID-19 as evidence shows that glucocorticoids reduce mortality in these patients.[8-10] However, glucocorticoids cause severe hyperglycemia and steroid-induced hyperglycemia (SIH) through multiple direct and indirect signaling on the glucocorticoid receptors in tissues of liver, muscle, bone and adipose tissue, and pancreatic β-cells.[11,12] This increases hepatic glucose production and adipose tissue lipolysis followed by increased insulin resistance, blocking of insulin action, decreased insulin production by pancreatic β-cells, and reduced glucose uptake by muscle and adipose tissue.[11,12] Even 1 week of glucocorticoid administration exacerbates hyperglycemia in people with diabetes (PWD) by increasing insulin resistance

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and impairing glucose homeostasis, and, thereby, increases their risk of complications.[11,13,14] In addition, the high inflammatory cytokine levels in moderate-to-severe COVID-19 further increase insulin resistance.[12,15] Severe hyperglycemia, SIH and its complications such as prolonged hospital stay, increased the severity of SARS-CoV-2, and mortality.[14] The unholy trinity of SARS-CoV-2, uncontrolled diabetes, and corticosteroids led to an increase in the deadly mucormycosis cases globally and in India, and other known hyperglycemic complications such as hyperglycemic hyperosmolar state (HHS) and diabetic ketoacidosis (DKA).[1,2,14]

Insulin is the recommended therapy for uncontrolled diabetes and SIH and is known to prevent complications in hospitalized patients with COVID-19.[13,14] Basal-bolus (BB) regimens have been recommended in hospitalized patients with COVID-19[13,16-18] and are the preferred choice for initiating insulin in hospitalized PWD with high sugars.[14,19] Basal insulin regimens are easy to titrate with the convenience of once daily dosing, ease of combining with BB regimens with minimal risk of hypoglycemia.[14,19-21] Ultralong-acting basal insulins such as insulin degludec (IDeg) additionally have the advantage of low glycemic variability and allow dosing and meal time flexibility.[19-21]

However, data on the efficacy and safety of initiating ultralong-acting basal insulins as part of BB regimen in PWD hospitalized for COVID-19 and SIH are scarce. This retrospective study helps bridge this gap on efficacy and safety of ultralong-acting basal insulins in these patients. Hence, this study was undertaken to analyze the efficacy and safety of an ultralong-acting basal insulin (IDeg) for managing SIH in PWD hospitalized for COVID-19.

## Materials and Methods

This was a single-center retrospective observational study. We retrieved and reviewed the medical records of PWD aged ≥18 years hospitalized at our center from September 2020 to November 2021 with a confirmed diagnosis of moderate-to-severe COVID-19. The patients were classified as moderate (scores 8–15) or severe (scores >15 to 25) COVID-19 based on their available computed tomography (CT) severity scores.[22] All patients were routinely treated with glucocorticoid therapy as per the COVID-19 protocol[8] during the study period. On hospitalization, all patients on steroids were routinely initiated with a BB regimen as part of their SOC and continued the same until discharge day. The patients who were initiated on IDeg as the basal insulin and human actaprid (HA) as the bolus insulin were included in the analysis. Baseline and day 7/discharge day data on hyperglycemia and medication status were analyzed. Data on hypoglycemia episodes (HEs) and other adverse events, such as HHS and DKA, were retrieved from medical records if reported during the hospital stay. The sigma plot version 15.0 was used to perform the statistical analysis, and a *P* value (<0.05) was considered statistically significant.

Since this is a retrospective study where data was collected using patient Electronic records, hence no ethical approval required.

## Results

The study included medical records data from 48 PWD and COVID-19 hospitalized at our center (27 men and 21 women; average age: 57.6 ± 13.4 years). Table 1 gives the baseline characteristics, including glucocorticoid dose and chest CT scores of all the patients.

The average fasting plasma glucose (FPG) on day 1 was 231.2 ± 91.1 mg/dL, and it reduced significantly to 150.7 ± 32.1 mg/dL on day 7/discharge ($P < 0.05$) [Figure 1]. The corresponding values for postprandial glucose (PPG) were 295.0 ± 118.4 (day 1) and 223.7 ± 65.4 mg/dL (day 7/discharge). The decrease in PPG was not statistically significant.

The average IDeg dose on day 1 and at day 7/discharge was 15.6 ± 5.0 and 20.1 ± 6.5 international units (IU), respectively [Figure 2]. The increase in Ideg dose was statistically significant ($P < 0.05$). Average dose of HA was 53.1 ± 16.7 IU on day 1 and 59.8 ± 16.6 IU on discharge day. The increase in HA dose was not statistically significant. No HEs, HHS, or DKA were reported in the medical records during hospitalization.

**Table 1: Baseline characteristics**

| Parameters | Values (±standard deviation where applicable) |
|---|---|
| Number of patients (*N*) | 48 |
| Male/female | 27/21 |
| Moderate COVID-19 (*n*; male/female) | 27; 17/10 |
| Severe COVID-19 disease (*n*; male/female) | 21; 10 males and 11 females |
| Age (years) | 57.6 ± 13.4 |
| Pulse (beats per min) | 87.2 ± 12.2 |
| Respiration (breaths per min) | 26.1 ± 10.1 |
| Blood pressure (mm/Hg) | 126.0 ± 12.5/78.9 ± 7.9 |
| Peripheral oxygen saturation ($SpO_2$) (%) | 93.8 ± 5.2 |
| Average Chest computed tomography scores across study population | 15.0 ± 6.3 |
| Severe COVID-19: average chest computed tomography score | 19.8 ± 3.4 |
| Average days of hospitalization | 6.8 ± 2.5 |
| Fasting plasma glucose (mg/dL) on day 1 | 231.2 ± 91.1 |
| Postprandial plasma glucose (mg/dL) on day 1 | 295.0 ± 118.4 |
| Injection dexamethasone dose (mg/day) (*n* = 35) | 17.3 ± 15.6 |
| Injection methylprednisolone dose (mg/day) (*n* = 11) | 80 ± 31 |
| Oral methylprednisolone dose (mg/day) (*n* = 2) | 8 |

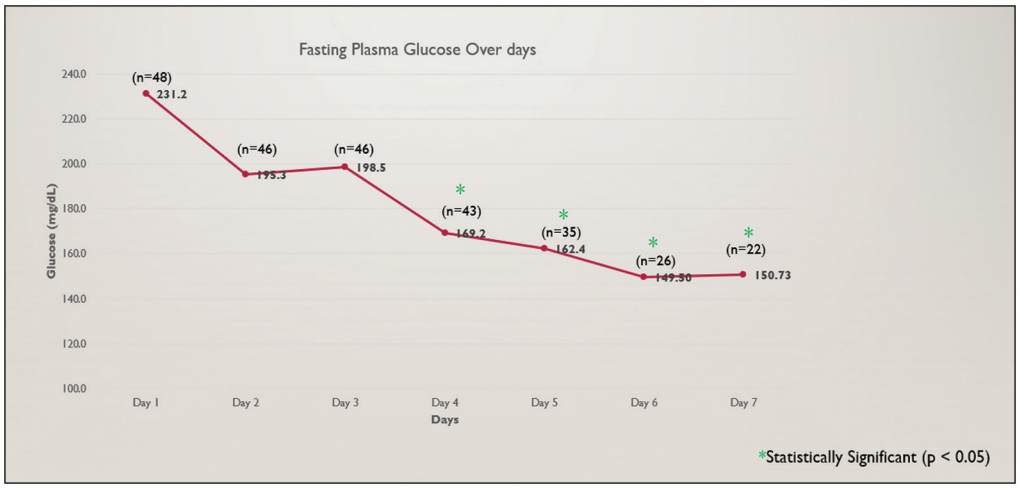


**Figure 1:** Fasting plasma glucose values from admission to discharge

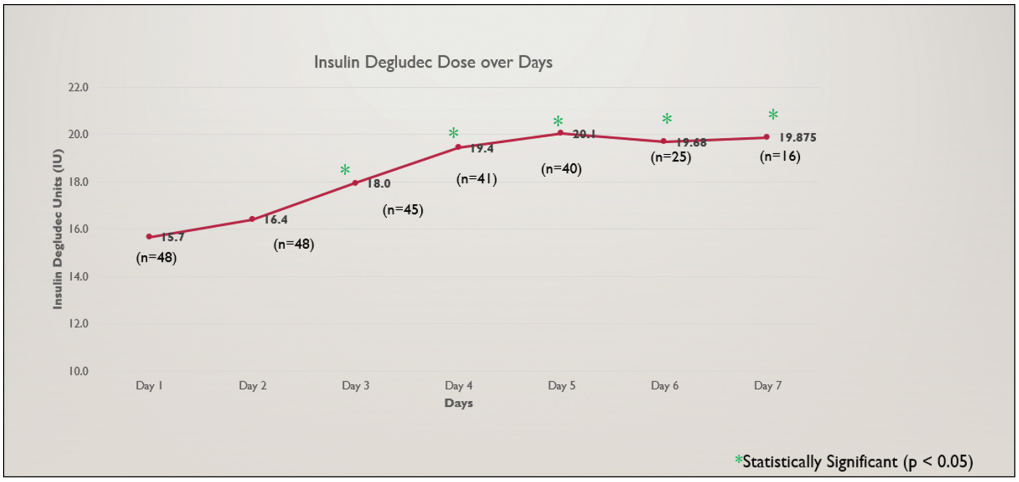


**Figure 2:** Insulin degludec dose from admission to discharge

## Discussion

This retrospective study shows that in PWD hospitalized for moderate-to-severe SARS-CoV-2 infection, who are on steroids can be effectively and safely treated with IDeg, an ultralong-acting basal insulin, with significant decrease in FBG and appreciable but insignificant decrease in PPG in a short span of 7 days. No HEs or any other adverse effects, such as HHS or DKA, were reported during this time.

Glucocorticoids are prescribed as SOC in moderate-to-severe COVID-19 as they reduce the risk of mortality.[8-10] The World Health Organization recommends the use of dexamethasone or prednisone or hydrocortisone for a period of 10 days in moderate-to-severe COVID-19.[14] The Indian Council of Medical Research guidance on the management of COVID-19 in hospitalized adults recommends the use of "methylprednisolone 1–2 mg/kg IV in two divided doses (or an equivalent dose of dexamethasone)" for 5–10 days.[8] However, it is a well-documented fact that the hyperglycemia associated with the use of glucocorticoid becomes worse in PWD.[15,23-25] The majority of patients in this study were on long-acting dexamethasone or intermediate acting methylprednisolone, which result in hyperglycemia throughout the day.[12] Hospitalized PWD, irrespective of COVID-19 status, who are treated with either long acting steroids or with high doses of steroids need basal insulins along with bolus insulins (BB regimen) to cover the day-long hyperglycemia.[14] Indian COVID-care facility guidance,[13] Endocrine Society of India position statement on managing SIH,[14] and other Western guidance on managing SIH in people with or without diabetes[15,16] usually recommend neutral protamine Hagedorn (NPH) insulin in hospitalized COVID-19 patients. However, with long- or intermediate-acting glucocorticoids, the hyperglycemia persists for 24 h. Therefore, NPH needs to be administered twice a day with a night time dose to cover the morning hyperglycemia.[15,16] To reduce the injection burden of basal insulins, a longer acting insulin is required to cover the fasting hyperglycemia the next day.[15,16] In such a situation, ultralong-acting basal insulin

like IDeg can be used for the basal component of the BB regimen recommended in hospitalized PWD with COVID-19, as it has low glycemic variability, covers day-long hyperglycemia with a single dose, and has low insulin variability and low risk for hypoglycemia and other adverse events such as HHS or DKA.[14,19,20]

There are limited data on the use of IDeg in PWD hospitalized for moderate-to-severe COVID-19 and SIH. However, IDeg has been found to be effective and safe in hospitalized PWD.[26-28] IDeg was found to be as effective and safe as insulin Glargine (IGlar) in hospitalized PWD in reducing mean daily blood glucose levels, with similar proportion of PWD in target blood glucose range, similar median length of hospital stay and complications.[26] However, the daily glucose variability is much lower with IDeg than IGlar, and thus, the glucose lowering response of IDeg is more predictable.[20,28,29] Also, IDeg has a much lower HE risk than IGlar.[20,28,29] In an observational study in hospitalized PWD, IDeg significantly reduced FPG ($P < 0.0001$), and had a very low HE incidence rate of 0.07 episodes per person-day.[28] These benefits come with the convenience of once daily dosing and meal timing and dosing flexibility[19,20] and provide a rationale for using IDeg as the ultralong-acting basal component of the BB regimen in PWD hospitalized for moderate-to-severe COVID-19 and SIH.

In this observational study, we found that a BB regimen with IDeg as the ultralong-acting basal component and HA as bolus component resulted in a significant decrease in FPG from 231.2 ± 91.1 mg/dL on day 1 to 150.7 ± 32.1 mg/dL on day 7 and decrease in PPG from 295.0 ± 118.4 on day 1 to 223.7 ± 65.4 mg/dL at discharge, in all PWD with moderate-to-severe COVID-19 and SIH. The steady state pharmacodynamic and pharmacokinetic profile of IDeg helps in a steady glucose lowering effect that is more evident initially on FPG than PPG.[20,21] Hence, IDeg causes a significant decrease in FPG and average blood glucose levels throughout the day.[20,21,26-28] No HEs, HHS, or DKA were reported in the medical records during hospitalization. There are no other IDeg studies in similar patient population. However, in another 7-day observational study, Fatati *et al*.[27] assessed the efficacy and safety of IDeg over a 7-day period in hospitalized PWD. They demonstrated a significant mean decrease in blood glucose from 210 ± 66.5 mg/dL on day 1 to 192 ± 48.6 mg/dL on day 7 and a significant decrease in glucose variability from 20% on day 1 to 9% on day 7.[27] There were no cases of severe or symptomatic hypoglycemia.[27]

Insulin intensification with higher doses of insulin are usually required to combat SIH in PWD with moderate-to-severe COVID-19.[15,30] This is because apart from the usual pathways of SIH,[11,12] high inflammatory cytokine levels during moderate-to-severe COVID-19 also contribute to the development of SIH.[12,15] This observational study too shows that a higher IDeg dose was required during the study to effectively control SIH from admission to discharge.

### Strengths and limitations

This small study of 48 PWD was limited by the biases associated with the retrospective design of the study such as missing data in the medical records, the type and dose of steroid used or dose and timing of short acting insulin or IDeg. Also, the study was limited only to the hospital stay and did not look at the course of IDeg use postdischarge. Further, the study was not powered to assess if the efficacy and safety of IDeg in controlling SIH was dependent on the mode of administration of steroids, type of steroid used, and dosage of steroid. The study also did not compare IDeg + HA with other BB insulin combinations.

Despite these limitations, this retrospective study showed that a longer acting basal insulin like IDeg can be used as the part of BB regimen recommend for hospitalized PWD with moderate-to-severe COVID-19 who developed SIH during admission. SIH was effectively controlled with no HE or hyperglycemia related adverse effects such as HHS or DKA.

## Conclusion

This retrospective study shows the effectiveness and safety of IDeg used in PWD hospitalized with moderate-to-severe SARS-CoV-2 who received high dose steroids. There was a significant decrease in FBG in a short span of 7 days with no HEs reported. Blood sugar was effectively controlled with no adverse effects such as HHS or DKA and hypoglycemia. However, this was a small short-duration study, and hence, longer duration and larger studies will be required to assess if this efficacy and safety of IDeg in hospitalized PWD with moderate-to-severe COVID-19 and SIH can be extrapolated to general PWD population developing SIH due to any cause.

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### Conflicts of interest

There are no conflicts of interest.

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